

PRoF Award abstract – Call 2016

The LimPrOn study

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1. Research Outline

| | |
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| Acronym | The LimPrOn study |
| Project name in English | The LimPrOn study: non-invasive early detection of high-risk pregnancies followed by remote monitoring. |
| Pitch (1 sentence) | The LimPrOn study is a project that will (1) focus on early detection of different clinical presentations related to pre-eclampsia, (2) help to improve clinical management and (3) open perspectives towards introduction of type-specific therapies, as well as prediction or even prevention of the syndrome. |
| Executive summary (max. 10 lines) | |
| <p>Our research, starting with a preconceptional screening or a first screening at 12 weeks of gestation, followed by an intensive telemonitoring program for those women at risk, could tribute to achieve a reduction of morbidity and mortality for both mother and child.</p> <p>A combination of impedance cardiography and electrocardiogram - Doppler ultrasonography is currently used as an early detection method of gestational hypertensive disorders and intra uterine growth retardation in pregnancy. Patients detected with a high risk for this disorders will be provided with telemonitoring devices which is a simple, safe and non-invasive tool to early interact on deviations on the normal values of the vital parameters of pre-eclampsia patients</p> | |

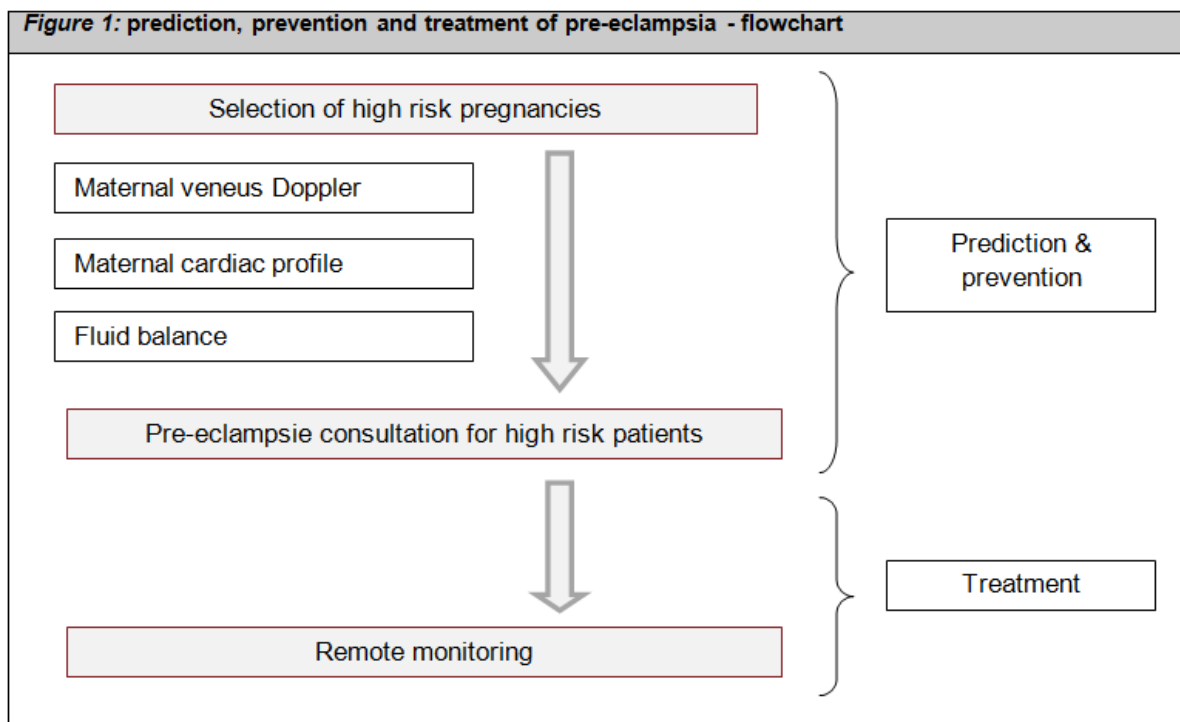
2. Cause and context of the research

Background

Worldwide, two to three percent of all pregnant women develop pre-eclampsia (PE). This is characterized by a high blood pressure and proteins in the urine after 20 weeks of gestation. PE remains a major cause for maternal, fetal and perinatal mortality and morbidity [1]. Until today, there is no treatment for pe; the only cure is the delivery of the placenta. Due to the need for a preterm delivery of the placenta and thereby the baby, there is more need for the newborn to get hospitalized in the neonatal intensive care. This means a higher mortality and morbidity rates for the newborns and lots of stress for the new parents [2].

This particular pregnancy pathology has been studied for more than 100 years, unraveling more and more details about the pathology. Despite our knowledge about PE is increasing, the ability to predict, prevent and treat PE still does not exist [3].

Our research focus on (1) the ability to predict and prevent PE, and (2) to treat this disease. The flowchart of this process is presented in figure 1 and will be further explained below.



(1) Prediction and prevention of PE

Until today, there is no non-invasive early detection method for PE in the first weeks of the pregnancy. It is in this critical period of the first weeks of the gestation that gestational hypertensive disorders result from maternal cardiovascular maladaptation to pregnancy [4-6]. Only when symptoms arise, a conclusive diagnosis is made. At this point, cardiovascular adaptations are already present [4-7].

The society lacks a real treatment to reverse the maladaptation. Only the present symptoms are managed by medication. **Easy non – invasive first trimester screening** would make **prevention** and prophylactic **treatment** possible and it would reduce the risk for PE with as much as 20 – 50% [8, 9]. Eventually, this will reduce the significant maternal and neonatal morbidity and mortality associated with PE.

Over the past years, our research group focused on this easy non-invasive screening tool, and examined profoundly the presence of PE in pregnant women. We gathered more and more information about gestational hypertensive disorders [10-13]. A combination of impedance cardiography (ICG) and electrocardiogram (ECG)-Doppler ultrasonography is currently used and studied as an early detection method of gestational hypertensive disorders and intra uterine growth retardation (IUGR) in pregnancy.

Our research group aims in the future at a clinical application of a completely new classification system for cardiovascular (dys)function using simple, easy-accessible and non-invasive methods, which allows identification of high risk pregnancies in the first trimester.

(2) Treatment of PE

During pregnancy, the women with symptoms of PE or which are at high risk for developing PE will be admitted to the maternal intensive care (MIC). This hospitalization has a serious emotional, economical social impact on the women and their relatives.

The reason of this hospitalization is to control the vital parameters of both the mother and the fetus and to ensure bedrest for the mother. Nevertheless, these actions can be performed without hospitalization, in the home environment of the pregnant women. But then, there is the lack of a midwife who will control her daily health.

To avoid this problem, **telemonitoring could offer the solution**. The women can stay at home, in her safe familiar setting and her health will be monitored at a distance. They

receive three medical devices (a blood pressure monitor, a weight scale and a activity tracker) with which they could control their parameters themselves. The data will be transmitted by Bluetooth and Wi-Fi to an online platform. The midwife in the hospital will daily review and evaluate this data in consultation with the gynecologist. When necessary, the pregnant women will be contacted.

By using this technique, an area of new benefits for the treatment of PE are possible:

1. Early signs of PE could be picked up and a **prophylactic treatment** will be possible.
2. A close **guidance of the anti-hypertensive drug treatment** is possible and changes in therapy can easily be made and followed.
3. A **reduction of the ambulatory out patients visits, in-house monitoring and/or hospital admissions** will be made.
4. A **better timing** of therapeutic interventions and/or labour induction is possible.

Aim of this project

This project aims to

- (1) focus on **early detection of different clinical presentations** related gestational hypertensive disorders and IUGR. This by using a combination of ICG and ECG-Doppler ultrasonography.
- (2) help to improve **clinical management** by using telemonitoring.
- (3) open perspectives towards introduction of **type-specific therapies**, as well as **prediction or even prevention** of PE.

References

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3. Innovation results achieved

(1) Prediction and prevention of PE

The study and data collection are still ongoing. A first article of the possibility to predict PE early in pregnancy has been published:

Oben, J., Tomsin, K., Mesens, T., Staelens, A., Molenberghs, G., & Gyselaers, W. *Maternal cardiovascular profiling in the first trimester of pregnancies complicated with gestation – induced hypertension or fetal growth retardation: a pilot study*. The journal of Maternal – Fetal & Neonatal Medicine, 2014. 27 **(16)**: p 6.

Cardiac, arterial, and venous function were evaluated in 242 pregnant women around 12 weeks of gestation, using ICG and ECG – Doppler ultrasonography. After postnatal determination of gestational outcome, first trimester measurements were compared between women with uncomplicated pregnancies (UP) and those who developed gestational hypertensive disorders (GHD) or normotensive fetal growth retardation (FGR).

Results are shown in table 1.

The conclusion could be made that maternal cardiovascular function in the first trimester of pregnancy differs between UP and those destined to develop GHD or FGR. This can be assessed with on-invasive maternal cardiovascular profiling, opening perspectives for the application of this technique in early gestational screening for GHD and FGR.

Table 1: First trimester combined ECG – Doppler and ICG measurements

| | FGR (n = 11) | p value | UP (n = 218) | p value | GHD (n = 13) |
|---|------------------|----------------|------------------|--------------|------------------|
| Age (years) | 29 (26–30) | 0.481 | 29 (27–33) | 0.727 | 30 (26–35) |
| Pregestational BMI (kg/m ²) | 23 (21–26) | 0.768 | 23 (21–27) | 0.023 | 27 (23–29) |
| GA delivery (weeks) | 39 (37–40) | 0.291 | 40 (39–40) | 0.005 | 38 (34–40) |
| Birth weight (g) | 2510 (2220–2700) | < 0.001 | 3404 (3105–3685) | 0.042 | 2970 (1701–3645) |
| Birth weight Percentile | 2.5 (2.5–5.0) | < 0.001 | 50 (25–62.5) | 0.170 | 25 (10–75) |
| Nulliparity | 90.91 | 0.011 | 52.29 | 0.361 | 61.54 |

Data are presented as medians (interquartile ranges) or percentages. Differences between groups are presented as *p* values (bold when significant at nominal level $\alpha = 0.05$) and were calculated using Mann–Whitney *U*-tests for continuous variables and Fisher's Exact test for categorical variables.

FGR, fetal growth retardation; UP, uncomplicated pregnancy; GHD, gestational hypertensive disorders (gestational hypertension and pre-eclampsia); BMI, body mass index; GA, gestational age.

Table 2. First trimester combined ECG-Doppler and ICG measurements.

| | FGR (n = 11) | p value | UP (n = 218) | p value | GHD (n = 13) |
|---|------------------|--------------|------------------|--------------|------------------|
| <i>Combined ECG-Doppler measurements</i> | | | | | |
| <i>Renal veins</i> | | | | | |
| Left RIVI | 0.45 (0.39–0.49) | 0.666 | 0.46 (0.38–0.55) | 0.913 | 0.46 (0.40–0.52) |
| Right RIVI | 0.44 (0.39–0.47) | 0.141 | 0.49 (0.39–0.56) | 0.282 | 0.52 (0.42–0.61) |
| Left PA/RR | 0.38 (0.29–0.40) | 0.086 | 0.31 (0.26–0.37) | 0.175 | 0.34 (0.30–0.42) |
| Right PA/RR | 0.33 (0.28–0.37) | 0.188 | 0.28 (0.22–0.34) | 0.641 | 0.29 (0.25–0.36) |
| <i>Hepatic veins</i> | | | | | |
| HVI | 1.34 (0.45–1.53) | 0.227 | 1.46 (0.70–1.60) | 0.983 | 1.47 (1.09–1.57) |
| Liver PA/RR | 0.19 (0.14–0.25) | 0.506 | 0.17 (0.13–0.23) | 0.983 | 0.17 (0.15–0.21) |
| <i>Uterine arteries*</i> | | | | | |
| Left RI | 0.69 (0.56–0.75) | 0.637 | 0.67 (0.57–0.76) | 0.480 | 0.66 (0.59–0.81) |
| Right RI | 0.55 (0.47–0.73) | 0.656 | 0.61 (0.50–0.71) | 0.084 | 0.77 (0.53–0.79) |
| Left PI | 1.06 (0.77–1.20) | 0.630 | 1.01 (0.79–1.23) | 0.463 | 0.99 (0.84–1.37) |
| Right PI | 0.76 (0.62–1.14) | 0.637 | 0.87 (0.67–1.10) | 0.080 | 1.26 (0.72–1.30) |
| Left QD/RR | 0.25 (0.22–0.41) | 0.766 | 0.27 (0.24–0.30) | 0.802 | 0.26 (0.23–0.30) |
| Right QD/RR | 0.25 (0.24–0.30) | 0.309 | 0.28 (0.25–0.30) | 0.927 | 0.28 (0.25–0.29) |
| <i>ICG measurements – standing position</i> | | | | | |
| <i>Pressures</i> | | | | | |
| SBP (mmHg) | 109 (103–134) | 0.614 | 114 (106–123) | 0.015 | 123 (113–129) |
| DBP (mmHg) | 74 (67–82) | 0.455 | 75 (71–81) | 0.011 | 82 (75–87) |
| MAP (mmHg) | 83 (76–94) | 0.522 | 85 (81–90) | 0.004 | 92 (87–98) |
| PP (mmHg) | 35 (31–46) | 0.470 | 38 (33–44) | 0.269 | 39 (38–44) |
| <i>Systolic output parameters</i> | | | | | |
| HR (beats/min) | 97 (86–101) | 0.986 | 94 (87–104) | 0.830 | 94 (88–100) |
| SV (ml) | 65 (58–75) | 0.033 | 75 (66–86) | 0.541 | 78 (66–100) |
| CO (ml/min) | 6.4 (5.4–7.3) | 0.025 | 7.1 (6.2–8.2) | 0.655 | 7.7 (6.0–9.1) |
| <i>Cardiac cycle time intervals</i> | | | | | |
| PEP (ms) | 95 (83–104) | 0.373 | 98 (89–108) | 0.479 | 103 (82–118) |
| PEPi (%) | 15 (12–17) | 0.401 | 15 (14–17) | 0.517 | 17 (14–19) |
| LVET (ms) | 243 (233–265) | 0.528 | 214 (229–258) | 0.197 | 248 (240–269) |
| LVETi (%) | 39 (38–41) | 0.287 | 38 (36–40) | 0.459 | 38 (37–41) |
| DT (ms) | 289 (264–326) | 0.890 | 295 (256–341) | 0.649 | 276 (256–332) |
| DTi (%) | 47 (43–49) | 0.996 | 46 (43–50) | 0.306 | 45 (43–49) |
| STR | 0.40 (0.32–0.43) | 0.299 | 0.41 (0.37–0.45) | 0.751 | 0.44 (0.32–0.48) |
| <i>Thoracic fluid parameters</i> | | | | | |
| TFC (l/k Ω) | 23.6 (22.7–25.0) | 0.169 | 24.9 (22.7–27.1) | 0.668 | 25.3 (23.3–29.6) |
| <i>Aortic flow parameters</i> | | | | | |
| VI (l/1000/s) | 70 (58–90) | 0.918 | 72 (62–82) | 0.016 | 57 (48–74) |
| ACI (l/1000/s ²) | 131 (105–182) | 0.892 | 133 (107–156) | 0.023 | 108 (67–135) |
| HI (Ω /s ²) | 24.9 (20.7–31.2) | 0.180 | 23.1 (19.2–26.9) | 0.019 | 17.3 (14.1–24.4) |
| TAC (ml/mmHg) | 1.8 (1.4–2.3) | 0.215 | 2.0 (1.7–2.3) | 0.603 | 2.0 (1.8–2.2) |

Data are presented as medians (interquartile ranges). Differences between groups are presented as *p* values (bold when significant at nominal level $\alpha = 0.05$) and were calculated using Mann–Whitney *U*-tests. FGR, fetal growth retardation; UP, uncomplicated pregnancy; GHD, gestational hypertensive disorders (gestational hypertension and pre-eclampsia); RIVI, renal interlobar vein impedance index; PA/RR, PA-time interval corrected for heart rate; HVI, hepatic vein impedance index; RI, resistive index; PI, pulsatility index; QD/RR, QD-time interval corrected for heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; PEP, pre-ejection period; PEPi, pre-ejection period corrected for HR; LVET, left ventricular ejection time; LVETi, left ventricular ejection time corrected for HR; DT, diastolic time; DTi, diastolic time corrected for HR; STR, systolic time ratio; TFC, thoracic fluid content; VI, velocity index; ACI, acceleration index; HI, Heather index; TAC, total arterial compliance.

*The number of evaluated subjects differs for measurements of the uterine arteries, $n = 7$, $n = 121$ and $n = 9$ for FGR, UP and GHD, respectively.

(2) Treatment of PE

A pilot project was ongoing from 1 January 2015 until 31 December 2015. 100 pregnant women were included in the study and 50 delivered before the first of January 2016. Of this 50 women, eight did have a low risk pregnancy and 42 a high risk pregnancy.

| | Control group: N = 8 | High risk group: N = 42 | P-value (2-paired) |
|-------------------------------|-------------------------|----------------------------|-----------------------|
| Age, yrs (SD) | 29.57 (4.89) | 30.42 (5.08) | 0.68 |
| Days participated, days (SD) | 72.57 (46.14) | 47.26 (42.68) | 0.15 |
| Length, cm (SD) | 167.28 (5.90) | 166.18 (6.81) | 0.68 |
| Pre-pregnancy weight, kg (SD) | 66.64 (6.67) | 74.23 (18.37) | <u>0.05</u> |
| BMI, m/kg (SD) | 23.29 (1.79) | 26.26 (6.07) | <u>0.01</u> |

Of this 42 women with a high risk pregnancy, 14 patients underwent an effective intervention because of the results collected by remote monitoring:

- 14 MIC admissions because of remote monitoring
 - o 3 women were diagnosed with gestational hypertension and received an anti-hypertensive drug treatment
 - o 8 women were diagnosed with PE and received an anti-hypertensive drug treatment or an induction.
 - o 3 women didn't have any clinical signs of gestational hypertension or PE
- 3 women started with an anti-hypertensive drug treatment after an ambulatory visit.

The demographics of the intervention and non-intervention group were as follow:

| | No intervention N = 28 | Interventions N = 14 | P-value (2-paired) |
|-------------------------------|---------------------------|-------------------------|-----------------------|
| Age, yrs (SD) | 30.64 (5.95) | 29.79 (2.94) | 0.61 |
| Days participated, days (SD) | 56.79 (47.34) | 26.36 (22.68) | 0.08 |
| Length, cm (SD) | 166.28 (6.55) | 166.00 (7.78) | 0.90 |
| Pre-pregnancy weight, kg (SD) | 74.03 (18.11) | 74.07 (20.10) | 0.99 |
| BMI, m/kg (SD) | 26.71 (6.02) | 26.76 (6.52) | 0.98 |

The measurements were as follow:

| | No intervention N = 28 | Intervention N = 14 | P-value (2 – paired) |
|---------------------------------------|---------------------------|------------------------|-------------------------|
| BP controls, n | 2123 | 939 | 0.80 |
| High, n (%) | 28 (1.31) | 316 (33.65) | 0.00 |
| Medium, n (%) | 216 (10.17) | 352 (37.48) | 0.00 |
| Normal, n (%) | 1879 (88.50) | 271 (28.87) | 0.00 |
| Expected BP controls, n | 3127 | 736 | 0.00 |
| Weight gain during pregnancy, kg (SD) | 3.34 (3.50) | 1.87 (1.86) | 0.08 |
| Weight controls, n | 911 | 167 | 0.00 |
| Expected weight controls, n | 1535 | 369 | 0.00 |

To conclude, the neonatal outcomes are presented below:

| | No intervention N = 28 | Intervention N = 14 | P-value (2 – paired) |
|-------------------------------------|---------------------------|------------------------|-------------------------|
| Sex, n (%) | | | 0.07 |
| Male | 14 (50.0) | 7 (50.0) | |
| Female | 14 (50.0) | 7 (50.0) | |
| Birth weight, g (SD) | 3325.89 (618.87) | 2842.14 (846.55) | 0.07 |
| NIC admissions, n (%) | 3 (10.71) | 5 (35.71) | 0.00 |
| NIC admissions because of PE, n (%) | 0 (0.0) | 1 (7.14) | 0.00 |

The following steps have been taken or are foreseen

1. Visualization of the maternal hemodynamics^a – **completed in 2013**
 - a. ECG – Doppler echography
 - b. Impedance Cardiography
 - c. Maltron BIOSCAN 920
2. Data collection of 1000 pregnant women at 12 weeks of pregnancy^a – **started in 2013 and completed in November 2015**
3. Development of an online dashboard which received the data performed by telemonitoring^b – **completed in December 2015**
4. Data collection of 100 pregnant women for a first pilot project in remote monitoring for high risk pregnancies^b – **completed in January 2016**
5. Start collaborations with seven other hospitals in Limburg. Set up a study protocol and flow chart, arranging medical devices and geographical settings to perform the inclusions of the external hospitals^c – **completed in February 2016**
6. Retrospective analysis of the pilot project to determinate the cost-effectiveness, accuracy and utility of remote monitoring in high risk pregnancies and the emotional wellbeing for the mothers^b (2016)
7. Start LimPrOn in cooperation with seven hospitals in Limburg^{a,b,c} (2016)
8. Retrospective diagnose of hypertensive disorders, PE or IUGR^a (2016)
9. Developing an algorithm to detect hypertensive disorders, PE or IUGR^a – (2016)
10. Validation of the algorithm by performing a second data collection^{a,c} (2016)
11. Validating the algorithm on his sensitivity and specificity^a (2016)
12. Inclusion of 1000 participants in LimPrOn^{a,b,c} (2017)
13. Further refinement of the flowchart and implementation of final flowchart in the Limburg hospitals (2017)

^aStudy about prediction and prevention of PE

^bStudy about treatment of PE

^cLimPrOn study

4. Link to the PRoF values

(1) Minimal comfort

Our most important contribution with this project is the positive impact on the psychosocial wellbeing for both the pregnant women and her relatives. She stays in her familial surroundings but her vital parameters will continue be monitored and evaluated. In this way, the women has an feeling of safety and a lot of stress-feeling will be avoided.

Also, by prediction PE and start with an prophylaxis therapy, less submissions on the NIC department will be necessary. This will have a positive impact on the emotional, economical social level of the mother and her relatives.

(2) Privacy & (3) security

The next steps are taken, in agreement with the HIPAA privacy and security standards, for protecting the application. First, the website of the application is protected by a SSL-certificate. This means that all the data between the patient and the website is encrypted. Secondary, a password, login and (30 seconds) authenticator are required for the healthcare professional to login on the application. Third, the data in the database is encrypted by AES-encryption. Fourth, there is an automatic IP-adres blocking systems for extravagantly request access. In addition, a team of ICT-specialists have secured the online platform and are standby in case of emergency. These steps guarantee optimal privacy for the patient.

(4) Anti-loneliness

Patients with a high risk pregnancy are a lot of times isolated from their social network. Once the diagnose is made, they need bedrest in the hospital and they stop with their social activities. One of the goals of this project is to stay as long as possible in their normal environment with the safety of continuous monitoring.

(5) Non stigmatizing solutions

Many mothers of premature born babies have feelings of guilt towards their neonate. They feel ashamed that their body couldn't care for the fetus until the due date and they have feelings of failure and uncertainty.

By anticipating on high risk pregnancies (by intense monitoring and medication prophylaxis), pregnancies can be prolonged and admissions to the NIC can be prevented.

(6) Inter-generational

The application of these techniques can only be applied by pregnant women. Nevertheless, anticipating on the fact that a woman has an high risk pregnancy can prevent long term complications (like cardiovascular diseases on older age for the mother, consequences of the preterm delivery for the baby, ...) for both mother and child.

The application of these techniques can be done by younger and older healthcare professionals.

(7) Respect

By compiling every person's personally risk profile for developing IUGR or an hypertensive disorder, qualified care will be become tailored to the patients' needs. Individual recommendations can be made, and every patient will be observed and evaluated regarding their own parameters. The researchers are also 24/7 available by phone or mail and even (unscheduled) face-to-face visits are possible. This will be perceived by the patient as a greater respect for their individual needs.

(8) Flexibility

Telemonitoring can be done in many different circumstances, settings and situations, and the recommendations/evaluations can adapt according to changes in symptoms or risk factors of the patients.



5. Applicable IPR rules

The intellectual property of this studie belong to the UHasselt, under the coordination of Prof. Dr. Wilfried Gyselaers.

6. Information on the partners

Eight hospitals in Limburg participate in recruiting patients: (1) Ziekenhuis Oost Limburg, (2) Jessa Ziekenhuis, (3) Sint Franciskus Ziekenhuis, (4) Heilig Hart Ziekenhuis, (5) Ziekenhuis Maas & Kempen, (6) Mariaziekenhuis Noord-Limburg, (7) Sint Trudo and (8) AZ Vesalius. The inclusion of the patients will be done in Ziekenhuis Oost Limburg and the UHasselt. The evaluation of the data and the cooperation of the interventions will be done in Ziekenhuis Oost Limburg.

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